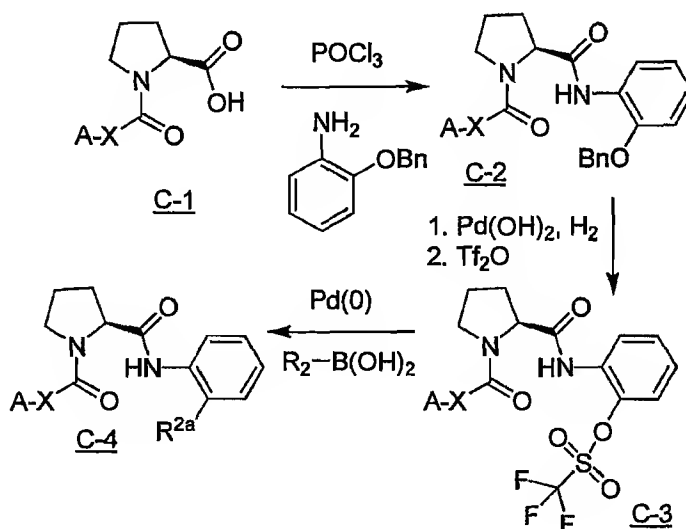


ATTACHMENT C

L-proline can be acylated under EDC-mediated coupling conditions to afford acylproline esters (B2). These esters can be hydrolyzed and further functionalized using a second EDC coupling using non-aromatic amines to generate the desired proline bis-amides (B-4).

REACTION SCHEME C

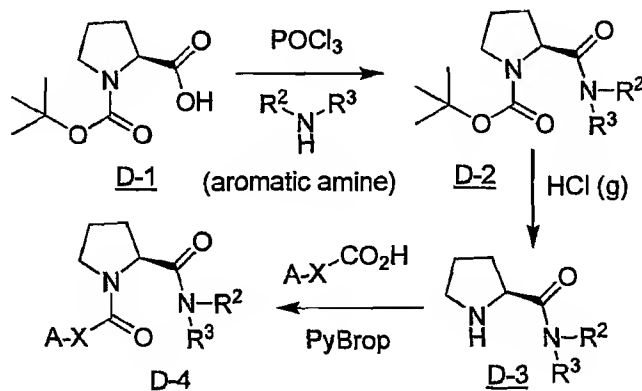


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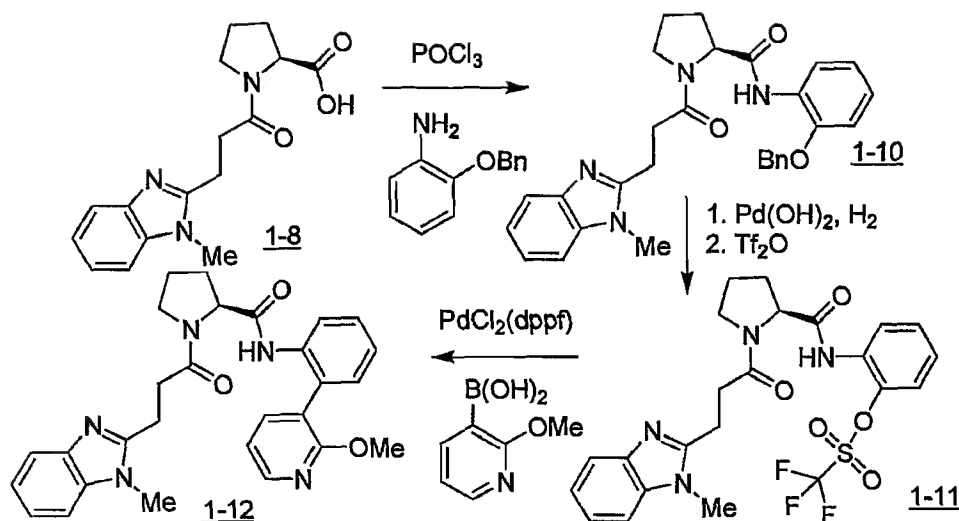
Acylated proline carboxylic acids (C-1) and 2-benzyloxylaniline can be coupled with phosphorous oxychloride to afford the anilide, C-2. This anilide can be deprotected under standard hydrogenolysis conditions and converted to the aryl triflate under the action of trifluoromethanesulfonic anhydride. Various boronic acids can be used in the subsequent Suzuki reaction to afford the desired proline bis-amides (C-4).

10

REACTION SCHEME D



Boc-L-proline can be reacted with an aromatic amine under the action of phosphorous oxychloride to afford protected anilides, D-2. These coupled products can be deprotected with gaseous



N-[2-(benzyloxy)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-10)

To a solution of 1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-proline (4.30 g, 14.26 mmol) and 2-(benzyloxy)aniline (2.84 g, 14.26 mmol) in pyridine at -10°C was added POCl₃ (1.43 mL, 15.69 mmol) and stirred for 0.5h. The system was warmed to 0 °C and quenched with 20 mL of ice-water, extracted with DCM, washed with water and dried over magnesium sulfate. The crude reaction mixture was purified using normal phase conditions (0%→8% MeOH(10% NH₄OH):DCM) to afford the title compound (1-10) as an orange foam. Data for 1-10: ESI+ MS [MH]⁺ C₂₉H₃₀N₄O₃ = 483.4.

N-(2-hydroxyphenyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-11; step 1)

To a solution of N-[2-(benzyloxy)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (2.60 g, 5.38 mmol) in methanol was added 20 wt% Pd(OH)₂ (1.3 g, 1.80 mmol) and stirred under a hydrogen balloon at room temperature. After 2h, the reaction contents were filtered through a pad of celite and concentrated to afford the title compound as a beige foam. Data for 1-11 (step 1): ESI+ MS [MH]⁺ C₂₂H₂₄N₄O₃ = 393.2.

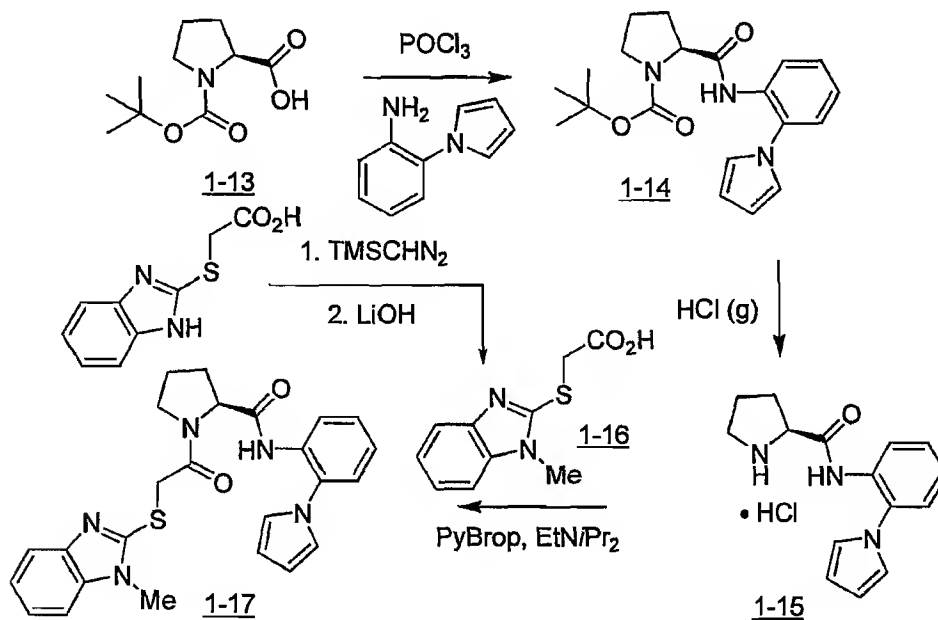
2-({1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)phenyl trifluoromethanesulfonate (1-11; step 2)

To a solution of N-(2-hydroxyphenyl)-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (2.10 g, 5.37 mmol) in pyridine at 0 °C was added triflic anhydride (0.995 mL, 5.91 mmol) and stirred for 0.5h. The system is extracted with EtOAc, washed with water and dried over magnesium sulfate. The crude residue was purified using normal phase conditions (0%→8% MeOH(10% NH₄OH):DCM) to afford the title compound (1-11) as a yellow foam. Data for 1-11: HRMS [M+H]⁺ C₂₃H₂₃F₃N₄O₅S calc'd 525.5228, found 525.1419.

N-[2-(2-methoxypyridin-3-yl)phenyl]-1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolinamide (1-12)

To a solution of 2-({1-[3-(1-methyl-1H-benzimidazol-2-yl)propanoyl]-L-prolyl}amino)phenyl trifluoromethanesulfonate (0.100 g, 0.191 mmol) and (2-methoxypyridin-3-yl)boronic acid (0.029 g, 0.191 mmol) in THF (1.0 mL) was added cesium carbonate (0.267 g, 0.820 mmol) and PdCl₂(dppf) (0.014 g, 0.019 mmol) and heated in a microwave to 160 °C for 10 minutes. The system was cooled to room temperature, extracted with EtOAc, washed with water and dried over sodium sulfate. The crude reaction mixture was purified using reverse phase conditions (5%→95% 0.1% TFA in water: 0.1% TFA in ACN) followed by free base extraction with saturated sodium carbonate to afford the title compound (1-12) as a white semi-solid. Data for 1-12: ¹H NMR (500 MHz, CDCl₃) δ 1.79-1.87 (m, 1H), 1.90-1.96 (m, 1H), 2.30-2.33 (m, 1H), 2.75-2.80 (m, 1H), 3.12 (m, 2H), 3.51 (m, 2H), 3.79 (m, 2H), 3.83 (s, 3H), 3.96 (s, 3H), 4.55 (m, 1H), 6.96 (m, 1H), 7.14-7.21 (m, 3H), 7.34-7.35 (m, 2H), 7.40-7.43 (m, 1H), 7.62 (m, 1H), 7.91 (m, 1H), 8.20 (br s, 1H), 8.64 (m, 1H). HRMS [M+H] C₂₈H₂₉F₃N₅O₃ calc'd 484.2270, found 484.2332.

EXAMPLE 4



1-(tert-butoxycarbonyl)-N-[2-(1H-pyrrol-1-yl)phenyl]-L-prolinamide (1-14)

Phosphorus oxychloride (468 μL, 5.11 mmol) was added to a stirring a solution of L-BOC-proline (1g, 4.65 mmol) and 1-(2-aminophenyl)pyrrole (735mg, 4.65 mmol) in dry pyridine (15mL). After 20 minutes the reaction was complete and quenched by slow addition of ice/water (50mL). The reaction was extracted with EtOAc, washed with saturated sodium bicarbonate and brine. The